Brain (2002), **125,** 2567–2578

Changes of non-affected upper limb cortical representation in paraplegic patients as assessed by fMRI

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Summary

Peripheral and central nervous system lesions can induce reorganization within central somatosensory and motor body representations. We report changes in brain activation patterns during movements of non-affected body parts in paraplegic patients with spinal cord injury (SCI). Nine SCI patients and 12 healthy controls underwent blood oxygen level dependent signal functional MRI during sequential finger-to-thumb opposition, flexion and extension of wrist and of elbow, and horizontal movements of the tongue. Single subject and group analyses were performed, and the activation volumes, maximum *t* values and centres of gravity were calculated. The somatotopical upper limb and tongue representations in the contralateral primary motor cortex (M1) in the SCI patients were preserved without any shift of activation towards the deefferented and deafferented M1 foot area. During finger movements, however, the SCI patients showed an increased volume in M1 activation. Increased activation was also found in non-primary motor and parietal areas, as well as in the cerebellum during movements of the fingers, wrist and elbow, whereas no changes were present during tongue movements. These results document that, in paraplegic patients, the representation of the non-impaired upper limb muscles is modified, though without any topographical reorganization in M1. The extensive changes in primary and non-primary motor areas, and in subcortical regions demonstrate that even distant neuronal damage has impact upon the activation of the whole sensorimotor system.

Keywords: cortical reorganization; upper limbs; spinal cord injury; fMRI

Abbreviations: COG = centre of gravity; fMRI = functional MRI; M1 = primary motor cortex; PMd = dorsal premotor areas; ROI = region of interest; S1 = primary somatosensory cortex; S2 = secondary somatosensory cortex; SCI = spinal cord injury; SMA = supplementary motor areas.

Introduction

Electrophysiological and functional neuroimaging studies in humans suffering from lesions of the peripheral (i.e. after upper limb amputation) and CNS (stroke) have shown that the adult brain is capable of extensive reorganization (Weiller *et al*., 1993; Kew *et al*., 1994).

Paraplegic patients with a traumatic spinal cord injury (SCI) present an acutely acquired neurological disorder with severe sensory and motor deficits caudal to the spinal lesion. They suffer from circumscribed spinal cord damage and show neurological deficits due to the disconnection of efferent motor and afferent sensory pathways between the lower body parts and the cortical and subcortical structures. This generates a special condition for the brain as the disconnected sensorimotor areas are preserved, but their efferent motor commands do not reach the effectors and no longer receive the appropriate afferent feedback.

How cortical and subcortical structures react to such a condition has been the subject of several investigations with various, partly divergent findings. On one hand, EEG in SCI patients has shown reorganization related to the recovery of limb functions with a posterior shift of cortical activation towards the primary somatosensory area (Green *et al*., 1998). On the other hand, transcranial magnetic stimulation (TMS) in paraplegics disclosed an enlargement of the cortical

Table 1 *Clinical data and neurological scores using the American Spinal Injury Association Impairment scale (ASIA) in all patients*

No.	Age/sex	Aetiology of the injury	Level of complete motor impairment	Time since injury (months)	ASIA	Motor (0–100)	Touch (0–112)	Pin prick (0–112)
1	23/M	transverse myelitis	L2	106	A	50	62	60
2	22/M	fracture Th9-11	L2	4	A	50	70	70
3	31/M	fracture L1	L2	5	A	50	82	82
4	31/M	fracture Th3/4	L1	4	A	50	44	42
5	25/F	fracture Th4/5	L2	76	A	50	56	56
6	43/M	fracture Th12	L4	10	B	56	98	84
7	34/M	fracture L1-3	L4	36	A	66	90	90
8	37/F	fracture Th7/8	L2	55	A	50	70	70
9	27/F	fracture L1/2	L2	66	A	53	80	74

The motor scores are assessed on a five-point scale across specific myotomes to calculate a single summary motor score. The touch and pin prick scores are assessed on a three-point scale at specific key points and summed to a single score (Maynard *et al*., 1997). M = male; F = female; A = no sensory or motor function is preserved; B = sensory but not motor function is preserved below the level.

representations of non-affected muscles in the primary motor cortex (M1), together with an increased excitability (Cohen *et al*., 1991*b*). In addition, PET in paraplegic and quadriplegic patients revealed extensive changes in cortical and subcortical activation during specific motor performances of the upper limbs (Bruehlmeier *et al*., 1998; Curt *et al*., 2002). Most investigations focused on changes in M1 without systematically addressing the somatotopical organization and the potential involvement of non-primary motor areas and subcortical regions.

The aim of the present study was to assess, using functional MRI (fMRI), how far the paraplegic condition in SCI patients can induce reorganization of brain activation during simple and well-controlled movements of the non-affected upper limb. Based on earlier findings (Bruehlmeier *et al*., 1998; Curt *et al*., 2002), we made the hypothesis that SCI with neurological deprivation of almost half the body should induce modifications in the representation of the non-affected upper limbs.

To test this hypothesis, we posed the following questions concerning paraplegic patients who had never experienced any functional impairment of their upper limbs:
(i) Are there any changes of the activation patterns in primary and non-primary sensorimotor areas during normal upper limb movements?
(ii) Is the distal to proximal somatotopical cortical representation of the upper limb modified?
(iii) Is there a shift of the upper limb representations into the adjacent regions devoted to the lower limb?

Material and methods

Paraplegic patients

Nine paraplegic patients (three female, six male, mean age 30.3 years ± 6.9, age range 22–43 years) were studied. Chapman and Chapman's handedness inventory revealed clear right-hand dominance in all patients (mean inventory scale 14.1) (Chapman and Chapman, 1987). The mean period following SCI was 40.2 months (range 4–106 months). The level of SCI was thoracic (n = 4) or lumbar (n = 5). Table 1 gives the age, sex, aetiology of the SCI, the level of complete motor deficit, the time since SCI and the neurological assessment using the impairment scale of the American Spinal Injury Association (ASIA) (Maynard *et al*., 1997) for the nine patients. None of the SCI patients had suffered a head or brain lesion associated with the trauma leading to the injury. Patients with uncontrollable spasticity-induced body movements were excluded from the study. Further exclusion criteria included seizures, any medical or mental illness, substance abuse, recurrent autonomic dysreflexia, dysaesthetic pain syndrome and use of medication known to alter neurological activity. The Glasgow Coma Scale (Teasdale and Jennett, 1974) after trauma was normal and the motor control of the fingers, wrist, elbow and of the tongue was unaffected in all SCI patients.

The study was approved by the local ethics committee, University Hospital, Zürich, and performed with the written informed consent of the patients.

Control subjects

Twelve healthy subjects (six female, six male, mean age 29.9 years ± 4.1, age range 25–39 years) without any history of neurological or psychiatric illness were recruited as control population. All had a right-hand dominance according to the Chapman and Chapman handedness inventory (mean inventory scale 13.2). Subjects gave written informed consent prior to the MRI examination.

Imaging procedures

Imaging was carried out on a 1.5 T whole body scanner (Signa Horizon, Echo-speed LX General Electric Medical Systems, Milwaukee, WI, USA) equipped with a standard product transmit–receive head coil. Foam padding and straps

were used to restrict head motion within the coil. T_1-weighted whole-brain anatomical reference volume data with an isotropic spatial resolution of 1.2 mm were acquired with a 3D spoiled gradient echo sequence [TE (echo time) = 9 ms, TR (repetition time = 50 ms]. Functional imaging was conducted using a gradient-echo echo-planar pulse sequence (TE = 40 ms, TR = 3750 ms, flip angle = 90°) sensitive to the blood oxygen level dependent (BOLD) signal. Thirty contiguous, axial slices with a slice thickness of 4 mm and covering the entire brain were acquired. The imaging matrix consisted of 128 × 96 data points resulting in a rectangular field-of-view of 256 × 192 mm and a nominal in-plane resolution of 2 × 2 mm. Series of 48 sequential volumes were acquired for each functional experiment.

Activation paradigms and manipulandum

Each activation experiment consisted of 30 s periods of rest alternating with 30 s periods of movement, repeated three times. The total data collection lasted 180 s. The beginning and end of each motor activation period were signalled with 'start' and 'stop' instructions verbally transmitted over the scanner intercom system. Prior to data acquisition, both patients and volunteers received written instruction about the experimental set-up. To ensure proper and reproducible task execution, each movement was practised first outside and then inside the magnet bore prior to the scanning procedure. During data acquisition, the movement performance was controlled visually by the examiner to monitor any movement or apparent change in the resting state of the non-moving limbs. Surface electromyography (EMG) during the fMRI experiments was not recorded as, due to gradient-induced artefacts, it lacks the sensitivity to detect small, undesired movements (Dai *et al*., 2001).

To assess within-limb somatotopy, three series of self-paced movements were performed at a rate of ~0.5 Hz in the following order: (i) repetitive flexion (40°) and extension (20°) of the right wrist; (ii) flexion (100°) and extension (–30°) of the right elbow; and (iii) repetitive, sequential finger-to-thumb opposition of the digits 2, 3, 4 and 5. Alternating right-left horizontal movements of the tongue were performed to locate the face representation, as other facial movements frequently produce movement artefacts.

An adaptable glass fibre forearm splint was designed to standardize the movements and thus allow for inter-subject comparisons. This splint was mounted at the height of the elbow on a rotation axis fixed onto the scanner table. It kept the forearm in a comfortable, slightly flexed position above the subject's abdomen and at an angle of ~35° relative to the scanner table. Strips and cast elements were applied between experiments (without repositioning the subject) to restrain movements of the wrist, hand and fingers. During the movements of a specific joint, potential movements of other joints were prevented by the use of additional devices and strips, e.g. blocking wrist and fingers during elbow movements. The movements of the tongue were unconstrained. The left arm was positioned along the body, and unintentional movements were restricted by the lateral wall of the magnet bore and by additional strips. During the experiments, the subjects closed their eyes and the light was dimmed in the scanner room.

fMRI data analysis

All data analysis and post-processing were performed offline as follows. To minimize artefacts due to residual head motion, functional volumes were realigned for each experiment using an automated image registration algorithm (Woods *et al*., 1998). Subsequently, data were spatially filtered using a 3D Gaussian convolution kernel of 4 mm full-width and half-maximum (FWHM). A fully automated procedure was used to register anatomical reference volumes to the Montreal average volumetric data set aligned with the Talairach stereotaxic coordinate system (Collins *et al*., 1994). The resulting transformation was used to resample the functional data into stereotaxic space.

The statistical analysis of the functional data was based on a linear model with correlated errors and was carried out for each dataset (Worsley *et al*., 1996). The design matrix of the linear model was first convolved with a gamma haemodynamic response function modelled as a difference of two gamma functions (Glover, 1999). Drift was removed by adding polynomial covariates in the frame times, up to degree 3, to the design matrix. Resulting effects and their standard errors were retained on a voxel-by-voxel basis. In a second step, sessions were combined using a mixed effects linear model for the effects (as data), with the standard deviations for fixed effects being taken from the previous analysis. A random effects analysis was performed by first estimating the ratio of the random effects variance to the fixed effects variance, then regularizing this ratio by spatial smoothing with a 15 mm FWHM filter. The variance of the effect was then estimated by multiplying the smoothed ratio by the fixed effects variance to achieve higher degrees of freedom. The threshold of the resulting *t* statistic images was obtained using the minimum given by a Bonferroni correction and based on a random field theory (Worsley *et al*., 1996). Spatially contiguous activated voxels were unified into individual clusters. Voxels that did not belong to a cluster of at least three voxels above the significance threshold were eliminated on the assumption that isolated activation was likely to be artefactual. The volume of activation, the maximum signal intensity (maximum *t* value) and the geometrical centre of gravity (COG) were determined for each cluster and their location in Talairach coordinates retained. Homogenous mass distribution in each cluster was assumed for the COG calculation; therefore, all voxels above the significance threshold were weighted uniformly. The COG calculation was preferred to activation maximum analysis, as COGs are less sensitive to random fluctuations and local signal-to-noise variations, and better represent shifts of extended activations. Furthermore, activation maxima have been shown to be

highly variable and relatively dependent evaluator-specific interpretations (Lotze *et al*., 1999).

Group analysis

The following four group comparisons were made on the basis of the linear model:

(i) In the control group, the activation patterns for each movement tested compared with rest ($P < 0.05$).

(ii) In the SCI patients, the activation patterns for the same movements compared with rest ($P < 0.05$).

(iii) Between the SCI and the control group, areas with significantly ($P < 0.05$) increased activation in SCI patients as compared with controls.

(iv) Between the groups, disclosing areas with significantly ($P < 0.05$) increased activation in controls as compared with SCI patients.

All the significant clusters of the resulting *t* maps were analysed with respect to the volume of activation, maximum *t* value and COG coordinates. These comparisons yielded the activation patterns for M1, non-primary motor areas, and other cortical and subcortical regions.

Quantitative analysis of primary motor cortex activation

To obtain detailed information on individual activations in M1, we performed a quantitative analysis at the single subject level as well as the group comparisons. As it is not possible to define anatomically the primary motor region precisely in the averaged group data due to cortical variability, this additional analysis was based on the activation maps in each individual subject. For this purpose, a trained neuroradiologist segmented manually a priori the contra- and ipsilateral M1 in each anatomical reference volume before analysis of the functional data and purely based on structural anatomy (shaded area in Fig. 1). M1 was anatomically defined as the cortex lying within the posterior wall of the precentral gyrus including the central sulcus and extending to the paracentral lobule. Although it is acknowledged that the exact anterior border of M1 cannot be defined solely on macroscopical landmarks, we determined the M1 as spanning the posterior two-thirds of the precentral gyrus (Geyer *et al*., 1996). These segmented regions were used as regions of interest (ROIs) for the quantitative analysis of the activated volumes for each movement and for each subject. Activated regions outside the respective ROIs were discarded for this analysis. The normal distribution of volumes of activation and COG locations within all single subject data and within the whole group of controls and SCI patients was assessed statistically by Kolmogorov–Smirnov tests. Potential differences in the localization of COGs (in the anterior–posterior, lateral–medial and cranial–caudal direction) and activated volumes for movements of various body parts within sessions were tested statistically using paired *t*-tests. In addition, potential differences between the standard deviations of the two groups were tested statistically by *F*-tests. Correlation coefficients between the three parameters and clinical scores (motor, touch and prick score), as well as the spinal level and the duration of impairment were calculated by using the Pearson–Bravais correlation. All statistics on single subject data were performed using the Statistical Package for the Social Sciences.

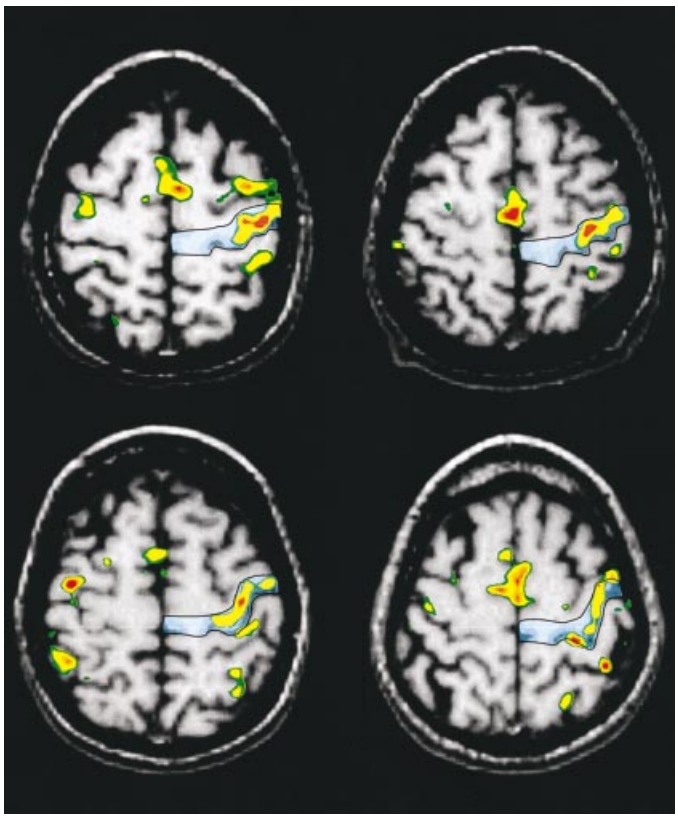

Fig. 1 Representative examples of four individual SCI patients during right finger movements demonstrated on axial slices through the omega-shaped portion of the central sulcus. The figure illustrates the medial and lateral expansion of the primary motor finger representation within the contralateral M1. The images furthermore display the manually segmented (shaded) M1 of the individual subjects. The manual segmentation procedure was performed a priori before the analysis of the functional data and was based purely on structural anatomy. Right on the sections corresponds to the left hemisphere.

Results

Activation patterns detected by fMRI

For the control population, the group analysis contrasting the on-condition (movement) with the off-condition (rest) revealed significant activation in many cortical and subcortical areas. During finger movements, contralateral activation was present in M1, the primary somatosensory area (S1), secondary somatosensory area (S2), the dorsal premotor (PMd) cortex and in the thalamus. The supplementary motor

Table 2 *Quantitative analysis of the volumes, maximum t-values and centres of gravity of the movement representations in the contralateral primary motor cortex in the SCI patients and in the controls*

Paradigm			Volume (mm^3)	Maximum *t*-value	Talairach coordinates of the centres of gravity		
					x	*y*	*z*
Fingers	SCI patients	Mean	4366	10.3	–37	–21	54
		SD	1320	1.4	3	4	5
	Controls	Mean	2972	11.1	–37	–20	58
		SD	1211	1.2	2	5	2
	t test		$P < 0.04$	n.s.	n.s.	n.s.	n.s.
Wrist	SCI patients	Mean	3978	11.1	–34	–23	57
		SD	934	0.7	3	4	5
	Controls	Mean	4409	10.6	–34	–23	59
		SD	2091	1.5	3	4	3
	t test		n.s.	n.s.	n.s.	n.s.	n.s.
Elbow	SCI patients	Mean	2987	10.6	–29	–26	60
		SD	1121	0.8	3	3	3
	Controls	Mean	2267	10.3	–29	–25	61
		SD	1158	1.3	4	4	5
	t test		n.s.	n.s.	n.s.	n.s.	n.s.
Tongue L/R	SCI patients	Mean	2470/1722	7.9/8.7	–52/56	–6/–7	33/32
		SD	1368/998	2.1/1.5	3/2	5/2	6/4
	Controls	Mean	3079/3042	9.2/8.7	–52/56	–5/–6	29/28
		SD	2034/1640	1.6/1.9	3/2	3/3	6/5
	t test		n.s.	n.s.	n.s.	n.s.	n.s.

The results of the statistical comparison between the two groups is indicated for each movement (*t*-test). L = left; R = right; n.s. = non-significant.

(SMA) and ventral premotor (PMv) areas were activated bilaterally. Activation was also detected in both anterior lobes of the cerebellum and was more pronounced on the right side, i.e. ipsilateral to the movement. During wrist, elbow and tongue movements, activation was seen in the same areas with additional bilateral activation in the superior parietal lobule, caudal cingulate motor areas (CMAs), the contralateral insular cortex and the putamen. Activation was present bilaterally in PMd and S2.

For the SCI patient population, the group analysis contrasting movement with rest showed statistically significant activation in the same regions.

Between-group comparisons

Both the quantitative analysis of individual somatotopical organization and the group analysis using the linear model converged in showing significant differences between the two populations. These included increased activity in several cortical and subcortical regions in the SCI patients compared with the controls.

Primary motor cortex

For the contralateral M1, the results of the quantitative analysis in the a priori defined ROIs are provided in Table 2. This lists the means and standard deviations of the activation volumes, maximum *t* values and Talairach coordinates of the COGs obtained for the various movements in the SCI patients and the controls. Statistical comparison between the data obtained from the two groups is also given. The SCI patients showed a significant enlargement of the activation volumes compared with the controls (4366 mm^3 versus 2972 mm^3; $P < 0.04$, paired *t*-test; Table 2). This difference was not related to the standard deviations as the *F*-test did not reveal any significant differences between the patients and the controls (SD = 1320 versus 1211; paired *t*-test: not significant). The enlargement of activation in the SCI patients did not correlate with the time since SCI, the level of injury or the motor, touch or prick score. These findings were confirmed by the group analysis contrasting the activation in the SCI patients with that in the controls. This is illustrated in Fig. 2, which displays the group analysis activation pattern in the SCI patients, the controls and the significant increase of activation in the SCI patients compared with the controls in representative axial, coronal and parasagittal sections. The enlargement of the contralateral M1 finger representation in the SCI patients is expanded both medially and laterally to the corresponding activation volumes in the controls.

During wrist, elbow and tongue movements, statistical comparisons of the volumes of activation in M1 did not reveal any significant differences between the SCI patients and the

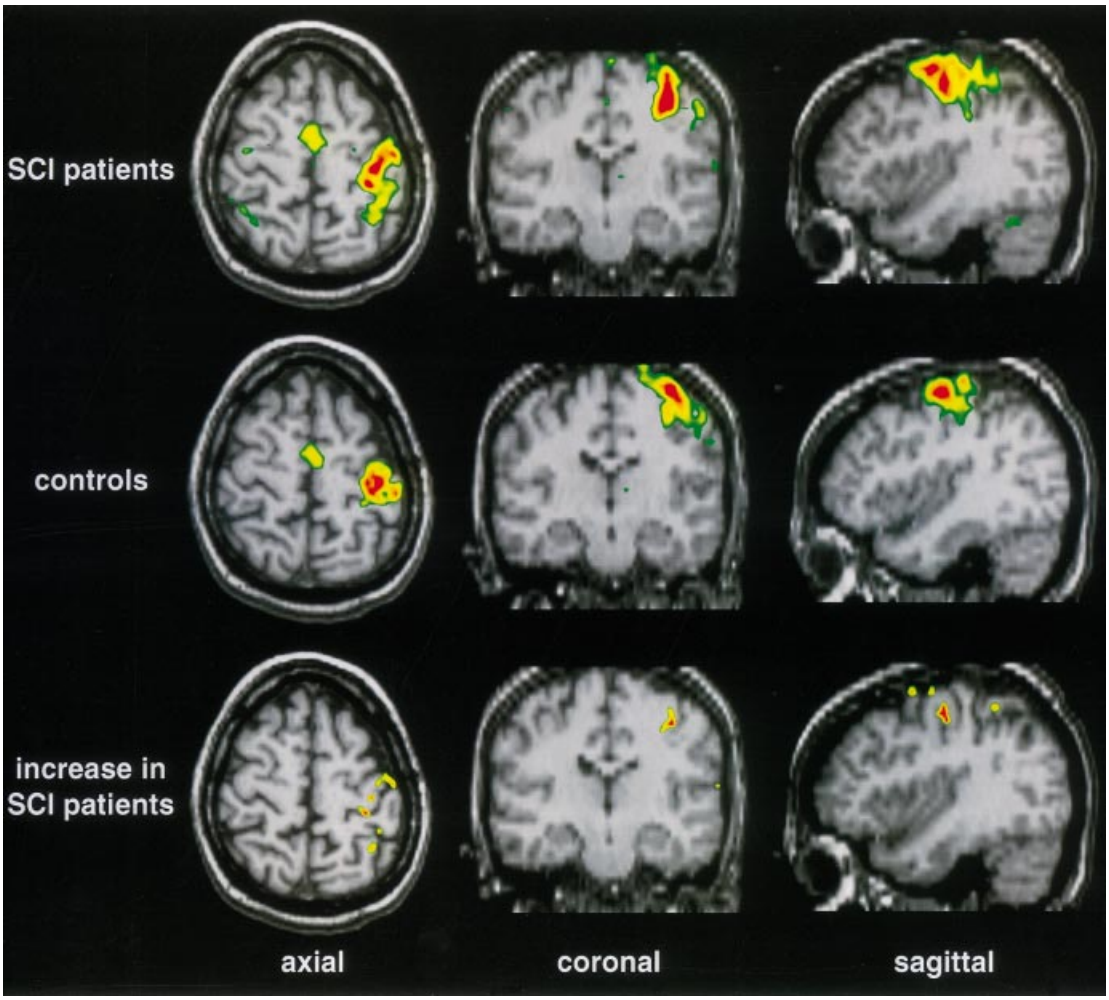

Fig. 2 Results of the group analysis for the finger movements demonstrating the activation in contralateral M1 on axial, coronal and parasagittal sections. Note the activation patterns in the SCI patients (*upper row*) and the controls (*middle row*), and the significant increase in activation in the SCI patients compared with the controls (*lower row*). The M1 finger representation is significantly enlarged in the SCI patients with a medial and lateral expansion of the volume. The additional increase in activation in the contralateral premotor and parietal areas is also statistically significant. Right on the sections corresponds to the left hemisphere. The same conventions apply as in Fig. 1.

controls (see Table 2). Specifically, no changes similar to those observed during finger movements could be detected. With respect to maximum *t* values, the quantitative comparisons obtained for all movements (including fingers) did not disclose any significant differences between the patients and the controls (10.3 $\pm$ 1.4 versus 11.1 $\pm$ 1.2; paired *t*-test: not significant).

To disclose potential differences between the somatotopical maps of the SCI patients and those of the controls, the mean COGs and SDs of the individual M1 body part representations were calculated over all subjects. The statistical comparison (paired *t*-test) between the COG coordinates obtained for all the movements tested in the two populations did not reveal any significant differences (Table 2). These findings are illustrated in Fig. 3, which displays in 2D scatter plot, the projections of all individual and mean COGs obtained for the four movements in the SCI patients in the axial and coronal plane. Figure 3 illustrates the somatotopical organization of the fingers, wrist, elbow and the left hemispheric tongue representation in contralateral M1 in the SCI patients. This is the same as that of the controls. No shift of activation towards the expected M1 foot representation was identified.

In the ipsilateral M1, the statistical analysis did not show any significant differences between the control subjects and the SCI patients, either for the maximum *t* values or for the volumes of activation and the COG coordinates.

Non-primary motor and parietal cortex, subcortical regions and cerebellum

To analyse whether activation changes occurred in regions other than M1, between group comparisons were performed contrasting the activation in the SCI patients with that of the

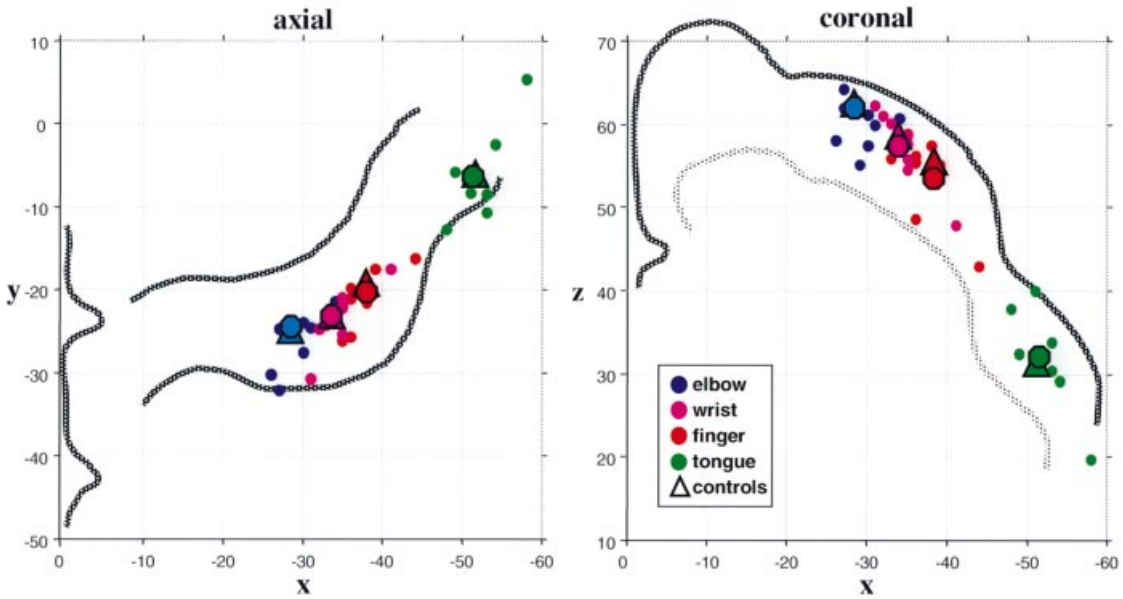

Fig. 3 Two-dimensional scatter plots of the individual COGs for the nine SCI patients in the contralateral M1 (small dots). The mean COGs of the patients are indicated by larger, encircled dots and the mean COGs of the controls by triangles. Note the intact somatotopical gradient of the within-arm and the left hemispheric tongue representations on both axial and coronal planes (with almost identical mean coordinates for all movements in the SCI patients and in the controls). Note also the absence of shift towards the deafferented and deefferented M1 foot area. *Left*: axial plane with approximate contour of the precentral gyrus. *Right*: coronal plane with cortical surface and limit to the white matter. *x*, *y*, *z*: coordinates corresponding to Talairach space (Collins *et al*., 1994).

controls. For the SCI patients, a statistically significant increase of activation was found in several non-primary motor areas, the parietal cortex and the cerebellum. Table 3 lists all clusters with statistically significant ($P < 0.05$) additional activation, considering both the increase in the *t* values and the volumes of activation. Table 3 also gives the COG coordinates of all these clusters, the corresponding cytoarchitectonic (Brodmann) and functional areas, the maximum *t* values and the activated volumes.

During finger movements, a significant increase of activation was detected in the ipsi- and contralateral SMA and PMd of the SCI patients. An increase was also found in contralateral S1, the superior parietal lobule bilaterally and the left inferior parietal lobule. Figure 4 demonstrates, on two continuous axial sections, the cerebellar activation in the controls, the SCI patients and the significant increase of activation in the SCI patients. Like the contralateral M1, the ipsilateral finger representation in the anterior lobe of the cerebellum was expanded in both anterior and posterior directions compared with the corresponding activated volume in the controls. An expansion was also detected in the smaller ipsilateral cerebellar finger representation and in the vermis on the right side (see Table 3).

Statistical differences between groups occurred more rarely for the other movements (Table 3). During wrist movements, an increased activation was found in the contralateral SMA, PMd, S1 and ipsilateral inferior parietal lobule in SCI patients. During elbow movements, a significant increase in the SCI patients was detected in the contralateral PMd, S1, superior parietal lobule and the precuneus. In contrast, no difference between the SCI patients and the controls was observed during bilateral tongue movements.

The inverse contrasts, i.e. between control subjects and SCI patients, did not disclose any areas of increased activation in the controls.

Discussion

The present investigation addressed the question of whether the cortical and subcortical representations of non-affected body parts are modified in complete paraplegic patients. Unlike several other studies, analysis of the fMRI data and the comparison with healthy subjects showed an unchanged M1 somatotopical organization for the upper limb and tongue, without any medial, lateral or posterior shift. However, differences in activation patterns between SCI patients and control subjects strongly suggest some reorganization. These included an increase in activation volume of the M1 hand representation and an additional activation in various non-primary cortical and subcortical regions for all forearm movements. These changes were most pronounced for the finger movements and were not related to any obvious modification in the motor performance of the upper normal limb.

Primary motor cortex

The most important result of the present comparison between paraplegics and healthy subjects was the increased activation volume in M1 during finger movements despite the preserved

Table 3 *Areas of statistically significant activation for finger, wrist, elbow and tongue movements in the non-primary motor and parietal areas and in the cerebellum of the SCI patients compared with the controls*

Paradigm	Side	Anatomical areas	BA	Functional areas	Talairach coordinates of the centres of gravity			Maximum *t*–value	Volume (mm^3)
					x	*y*	*z*		
Fingers	R	Superior frontal gyrus	6	SMA	1	1	65	6.0	176
	R	Superior frontal gyrus	6	SMA	4	–15	51	5.9	128
	R	Superior frontal gyrus	6	SMA	9	5	50	6.3	112
	L	Superior frontal gyrus	6	SMA	–3	–3	72	5.6	64
	L	Precentral gyrus	6	PMd	–34	–10	65	8.6	390
	L	Precentral gyrus	6	PMd	–46	–7	56	6.5	384
	L	Middle frontal gyrus	6	PMd	–37	1	64	6.6	240
	L	Superior frontal gyrus	6	PMd	–16	–8	72	6.1	160
	R	Precentral gyrus	6	PMd	42	–14	65	6.0	128
	R	Precentral gyrus	6	PMd	47	–2	44	5.5	112
	L	Post-central gyrus	3	S1	–34	–28	57	7.7	320
	L	Post-central gyrus	3	S1	–17	–34	76	5.9	144
	L	Superior parietal lobule	5		–37	–41	60	5.2	64
	R	Superior parietal lobule	7		29	–49	46	6.4	272
	R	Superior parietal lobule	7		22	–68	50	6.2	224
	L	Superior parietal lobule	7		–10	–57	72	5.3	64
	L	Inferior parietal lobule	40		–37	–49	53	6.4	272
	L	Inferior parietal lobule	40		–43	–40	56	5.8	64
	R	Cerebellum			21	–70	–19	6.6	416
	R	Cerebellum			18	–49	–24	6.5	144
	L	Cerebellum			–28	–70	–23	5.2	64
	R	Vermis			4	–75	–18	5.7	224
Wrist	L	Superior frontal gyrus	6	SMA	–3	5	52	5.4	64
	L	Precentral gyrus	6	PMd	–29	–11	72	8.7	240
	L	Paracentral lobule	5	S1	–3	–39	75	6.9	256
	R	Inferior parietal lobule	40		62	–40	40	5.7	64
Elbow	L	Precentral gyrus	6	PMd	–28	–12	72	8.8	192
	L	Post-central gyrus	3	S1	–11	–34	76	7.2	560
	L	Superior parietal lobule	5		–24	–44	69	5.8	112
	L	Precuneus	7		–6	–46	70	6.6	208
Tongue	–	–	–	–	–	–	–	–	–

BA = Brodmann area; L = left; R = right.

within-upper limb representation. The enlargement of the M1 finger region confirms a preliminary report by Turner and colleagues, who described a slightly larger hand representation in SCI patients (Turner *et al*., 2000). It is also in line with TMS investigations in paraplegics showing an enlarged representation of the preserved muscles proximal to the lesion level (Cohen *et al*., 1991*a*; Streletz *et al*., 1995).

The maps of the COGs in the within-upper limb representation and the relation to the tongue region were not different in paraplegic patients and control subjects (Kleinschmidt *et al*., 1997; Alkadhi *et al*., 2000). This finding differs strongly from that of a fMRI study in four paraplegic patients showing a displacement of the activation maxima for elbow movements in the direction of the disconnected lower limb region (Lotze *et al*., 1999). This discrepancy with our present findings can be attributed to differences between the two paraplegic populations and/or to the fMRI methodology used. In our investigation, all paraplegic patients suffered from traumatic and complete SCI lesions whereas the subjects of the other study mostly had lesions of various aetiologies. With respect to methodology, we used the COG method to locate topographically the activations instead of merely measuring activation maxima. We consider the COGs as the most reliable method for describing cortical body representation; this conclusion is in line with a later publication by the same group (Lotze *et al*., 2000). Furthermore, a preserved normal somatotopy in quadriplegic SCI patients moving or attempting to move several body parts was reported recently (Shoham *et al*., 2001). The latter findings are not quite in line with TMS studies in quadriplegic patients reporting an enlargement together with some lateral shift of the excitable area for the abdominal muscles and for the biceps brachii (Levy *et al*., 1990; Topka *et al*., 1991).

Non-primary motor areas

Another important and new finding from our study is the significant increase of activation in several premotor (SMA,

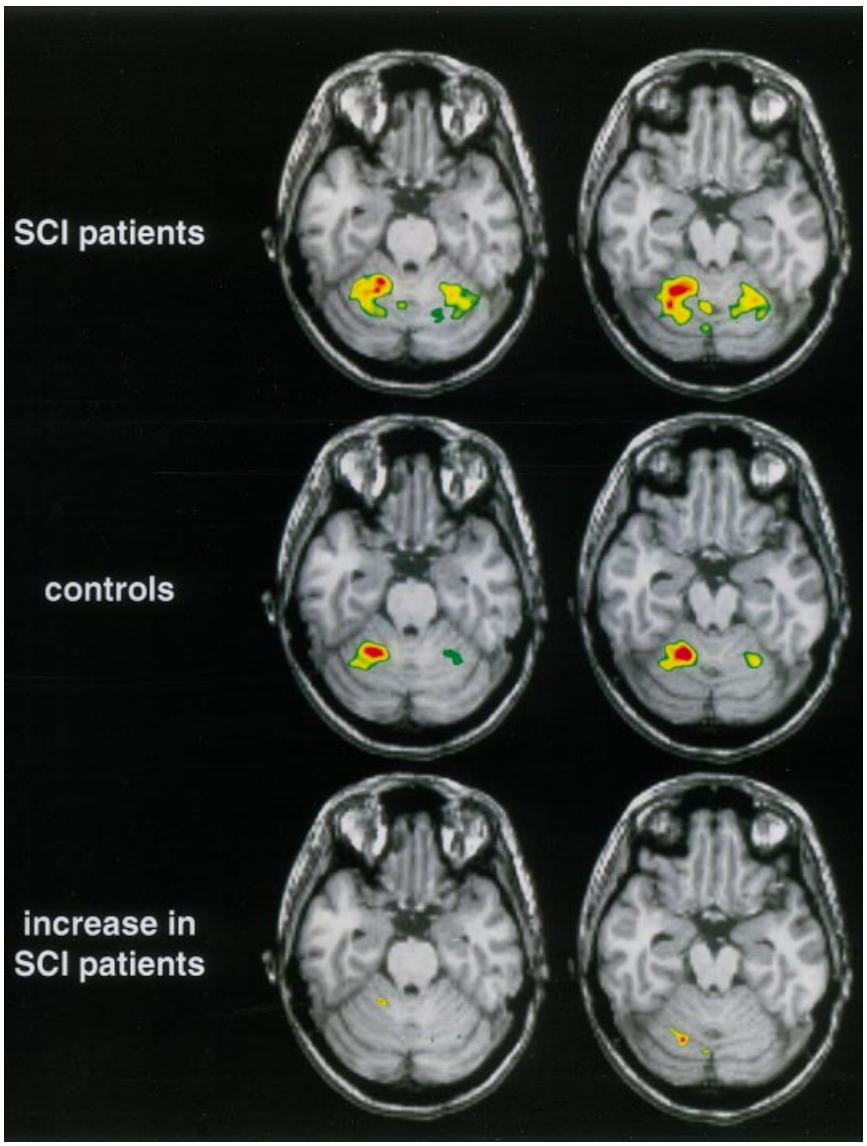

Fig. 4 Results of the group analysis for finger movements demonstrating the cerebellar activation in two continuous axial sections in the SCI patients (*upper row*), the controls (*middle row*) and the statistically significant increase of activation in the SCI patients (*lower row*). The ipsilateral cerebellar finger representation in the SCI patients is enlarged compared with the controls. A less prominent expansion is also seen in the contralateral cerebellar anterior lobe and in the right paramedian vermis. The same conventions apply as in Fig. 1.

PMd), post-central and parietal cortical areas, as well as in the anterior cerebellum for movements of the intact upper limb. This change in the degree of activation was most frequent and prominent for finger and hand movements. Similar changes have been shown with PET in paraplegic and tetraplegic SCI patients in a task requiring the manipulation of a joystick and during wrist extension (Bruehlmeier *et al*., 1998; Curt *et al*., 2002). Our findings demonstrate that an interruption of the spinal pathways induces representational modifications of the non-impaired body parts in non-primary motor areas. Traditionally, these areas have been associated with the initiation (Vidal *et al*., 1995) and planning (Deiber *et al*., 1996) of motor performance, but they have recently been shown to also participate in simple movements (Fink *et al*., 1997; Kollias *et al*., 2001).

There are several potential explanations for our findings. One possibility is that the spinal lesion induces changes in the afferent pathways to the non-primary cortical areas through the cerebellum, basal ganglia and thalamus (Orioli and Strick, 1989; Rouiller *et al*., 1999). Another possibility is that the enlargement of the hand representation in M1 provokes, via the existing corticocortical connections, an increased activation in PM, SMA, post-central and parietal cortex (Stepniewska *et al*., 1993; Wise *et al*., 1997; Rizzolatti

et al., 1998). Although the present fMRI methodology cannot opt for one of the two possibilities, a striking observation is the fact that most changes observed in the non-primary motor cortical regions occurred for the finger and hand movements, and thus could well be secondary to the expansion of the M1 hand representation. The significant modifications disclosed in non-primary motor cortical areas and in the cerebellum demonstrate that the whole sensorimotor network involved in the control of limb movements can be subject to reorganization after interruption of the afferent and efferent spinal pathways.

Origin of the brain activation changes

The question of whether the modifications in brain activation could be an artefact caused by the motor performance can be ruled out. Movement amplitude, repetition rate and strength of muscle contraction (which have been shown to influence brain activation) were well controlled in the present investigation and were similar for control subjects and SCI patients (Dettmers *et al*., 1995; Blinkenberg *et al*., 1996; Schlaug *et al*., 1996; Williamson *et al*., 1996; Waldvogel *et al*., 1999). Use-dependent changes in the M1 forearm representation have been demonstrated in monkeys (Nudo *et al*., 1996) and motor cortex plasticity during motor learning has been shown repeatedly in human subjects (Karni *et al*., 1995; Pascual-Leone *et al*., 1995; Pearce *et al*., 2000). It is unlikely that the changes in brain activation in our SCI patients were induced by increased use of the upper limbs, as only the volume of the M1 hand representation was increased and not that of other normal upper arm muscles, as would be expected due to their overuse. Furthermore, we can exclude a learning or training effect since only simple repetitive movements were required.

The observed changes in brain activation may be induced by changes either at the spinal or cortical level, or both (Raineteau and Schwab, 2001). At the spinal level, sprouting or rewiring may occur close to the SCI segments and consequently induce an enlargement of the cortical representation of the muscles innervated by the motor neuronal pool just rostral and adjacent to the lesion. In accordance to this, only the representation of the hand and finger muscles was enlarged in the present study; their motor neuronal pools are located in the lower cervical and upper thoracic spinal grey, thus closer to the SCI levels than the motor neurones of more proximal muscles. The higher excitability observed in TMS studies could also be one of its consequences (Topka *et al*., 1991; Streletz *et al*., 1995). At the cortical level, an expanded hand representation may be caused by changes in intracortical connectivity or by sprouting of cortical connections in the absence of peripheral afferent inputs to M1 (Jacobs and Donoghue, 1991; Florence *et al*., 1998; Sanes and Donoghue, 2000). The influence of afferent input in long-term reorganization of the human motor cortex is supported by several investigations (Hamdy *et al*., 1998; Ridding and Rothwell, 1999). In our study, the most extensive changes in brain activation occurred during finger and hand movements. The hand has, together with the mouth, the largest cortical representation compared with that of proximal, axial and lower limb muscles, and the highest density in sensory receptors. The present data may indicate that the extent of cortical reorganization is influenced by the functional significance of the motor output projections and of the afferent feedback. Brain imaging alone cannot distinguish whether the observed changes are induced at the cortical or spinal level, nor provide definitive information on the underlying pathophysiological mechanisms responsible for these changes.

Conclusion

The extensive activation changes in the cortical and subcortical representation of non-affected muscles after remote spinal lesions demonstrate that even distant neuronal damage affects the function of the whole CNS. This hypothesis was proposed at the beginning of 20th century and termed ‘diaschisis’ by Constantin von Monakow (Kesselring, 2000). Our findings in paraplegic patients disclose the complex changes in the CNS organization after a neuronal lesion and strongly suggest that distinction should be made between the reorganization induced by a new general body condition and that related to functional impairment.

Acknowledgements

This work was supported by the Swiss National Research Program NRP 38 4038–052837/1, the NCCR on Neural Plasticity and Repair, and by Swiss National Science Foundation grant 3152–062025.

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Received April 9, 2002. Revised June 9, 2002.
Accepted June 13, 2002